response, is formulated for parenteral administration and comprises

said at least one antigen being overrepresented on the prostate gland with respect to other tissues or an immunologically effective portion thereof,

wherein said [ingredient] antigen is encapsulated in or coupled to a liposome.

Remarks

Claim 21 has been amended to place it in a better condition for allowance or appeal; it has simply been clarified to contain language consistent with the remaining claims. No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention resides in the concept that an immune response mounted by a subject against the subject's own tissue, where that tissue is host to unwanted tumor cells, is a method to inhibit the growth of the tumor *per se*. This concept is nowhere suggested in the art; indeed, the very problems noted by the Examiner associated with use of tumor, as opposed to host, tissue antigens to elicit an immune response are obviated by the methods of the invention. Thus, the claims are directed to methods to induce an antitumor immune response by eliciting a response to the host prostate tissue (claims 1-7) and to pharmaceutical or veterinary vaccines for this purpose.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Applicants appreciate the withdrawal of the previous rejection of claims 1-40 under 35 U.S.C. § 101; however, the substance of the rejection made under 35 U.S.C. § 112, first paragraph, appears also to be grounded in

doubts that the methods and compositions, admittedly fully described and taught, will actually function in accordance with the description. The basis for the rejection appears to be the absence of any *in vivo* clinical data; the asserted lack of evidence that establishes the efficacy of the invention as claimed; and the failure of others to provide successful vaccines eliciting an antitumor immune response using tumor antigens. There is no rationale that would provide a basis to conclude that the written description is inadequate or that the best mode is not disclosed.

With respect to the first two bases on which this rejection is made, it is respectfully submitted that the position of the Office is not in accord with the legal standards for protection of inventions of this type. The recently decided case of In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) is believed controlling. With respect to the third basis, the conclusion advanced does not result from the argument.

In Brana, the claims were directed to compounds asserted to have antitumor activity. The claims were rejected, as are the claims here, under 35 U.S.C. § 112, first paragraph. The court recognized that the rejection could equally have been made under 35 U.S.C. § 101, as it questioned not the words of the teaching *per se*, but rather whether the stated utility for the compounds was in fact correct. The court further took note of the recently issued Guidelines for Biotechology applications as related to utility; the holding in Brana is consistent with these Guidelines. (See page 1439 of the Opinion).

In the Opinion, the court made clear that the kinds of concerns raised by the Office in this case do not legitimately address the issues that would be relevant to a rejection under 35 U.S.C. § 112/101. As the court said at page 1442,

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful as well before it is ready to be administered to humans.

While the applicant in Brana included *in vitro* and animal model tests in the specification, the court did not hold that such tests are necessarily required. Instead, the court quoted from In re Marzocchi, 169 USPQ 367 (CCPA 1971) to the effect that the statement in the specification related to utility "must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements."

In the present application, the applicant describes in detail at pages 15-17 the use of the compositions of the invention to immunize a subject with respect to prostate cancer. There is no reason advanced to support the conclusion that one of ordinary skill would doubt the efficacy of the protocols described, other than the kinds of physiological effects irrelevant to the basic pharmaceutical utility of the compositions that are the concern of clinical approval. In other words, the rationale provides no basis to doubt the fundamental pharmacological activity, but rather addresses side issues having to do with approval for use in the clinic.

With respect to the assertion that other people using other methods have been unsuccessful in consistently producing successful anticancer vaccines, applicants fail to see the logic of this argument. Applicants' method is different from those of the prior art and that is why an application for patent is being made. Prior failures using

other techniques -- in this case using antigens derived from tumor cells as opposed to those derived from host cells of the organism which accommodates the tumor -- are irrelevant to the success or failure of applicants' invention.

With respect to the assertion that the scope of the antigens claimed is too broad, this basis for rejection is respectfully traversed. The Office seeks to limit the antigens includible in the vaccines to PSA, PSMA AND PAP since these are the only prostate related antigens specifically mentioned in the specification. However, this limitation appears unfounded. The invention resides in recognizing that any antigen that is overrepresented on the host tissue, prostate, is useful in such vaccines. Applicants do not claim to have discovered and characterized such antigens themselves, rather they are dependent on others in the art to make such identification. As other antigens associated preferentially with the prostate are identified, it is reasonable to include them within the scope of the invention, since the invention lies not in the discovery of the antigens themselves, but rather in a method to employ any antigen over represented on the prostate.

There is no assurance that all of the antigens overrepresented on the prostate have already been discovered. As evidence of this, Applicants enclose **(reference)** which describes an antigen newly discovered as associated with prostate tissue-prostate specific mucin. Applicants, of course, do not claim this antigen *per se*, but rather only the method of using it (or any other prostate specific antigen), which method of use is the invention of applicants.

It is believed that the scope of the invention is appropriate according to the standard set forth in In re Marzocchi 169 USPQ 367 (CCPA 1971) where claims supported by either working examples or broad language in the

specification are presumed to be supported. Only by showing, in a *prima facie* case, that one of ordinary skill in the art would refuse to believe the statements in the specification may the Office discount them. There is no rationale supplied to doubt that other prostate associated antigens, as they are discovered, would work in the vaccines as well as the already described antigens PSA, PAP and PSMA. It does not appear that a *prima facie* case has been made out as to question the claim scope, and this basis for rejection may properly be withdrawn.

In view of the foregoing, the entire rejection under 35 U.S.C. § 112, first paragraph, may properly be withdrawn.

The Rejection Under 35 U.S.C. § 112, First and Second Paragraphs

The Office objects to the term "at least one antigen overrepresented in the prostate gland," "peptide"; "portion [sic, protein?]" as vague and indefinite. These particular terms have been removed from the claims.

Other terms objected to relate to "fragments" or "portions" of the antigens which, according to the office, would include embodiments in the scope of the invention that would require undue experimentation to produce.

Reconsideration of the objection to these terms is requested. With respect to the antigen *per se*, it is well known that immunogenicity of whole proteins, such as PSA, PSMA and PAP, resides only in the epitope-bearing regions of the molecules. It is well established that less than the complete molecule would be required to obtain a successful response. It is, of course, not necessary to produce all possible fragments; the intent of the claim is simply to include the embodiments that would be arbitrarily chosen by

anyone of ordinary skill -- the option of using less than the complete protein.

With respect to fragments of the antiidiotypic antibody, the possibility of using immunologically effective fragments is well understood. It is well known in the art that the immunospecificity of an antibody resides in the variable regions and that a complete immunoglobulin is unnecessary to elicit an immune response vis-à-vis the antiidiotypic portion. It is conventional to use, for example, Fab, Fab', and the like where additional functionality is not required.

In summary, the objection to the language in the claims which indicates that less than a complete antigen or less than a complete antiidiotypic antibody can be included within the scope of the invention appears unjustified. Those of ordinary skill in the art are well aware that neither a complete antigen nor a complete antibody is required for immunogenicity or to provide the correct epitope.

In specific response to this point of objection, it is unnecessary for the application to provide a disclosure of all possible vaccine derivatives (i.e., portions) nor is it necessary to provide evidence that all such derivatives would be therapeutically effective. What is well known to those of ordinary skill need not be taught. See, for example, In re Skrivan, 166 USPQ 85 (CCPA 1970). It is well known in the art that a fragment may substitute for the whole. Furthermore it is not necessary to use fragments in order to practice the invention. The claims should not be avoidable by the simple expedient of using less than the complete antigen or antibody. One of ordinary skill would know which fragments are too small or too hydrophobic, for example to be likely to work.

The further citation to Ezell critical of the use of tumor-derived antigens as vaccines appears irrelevant to this objection. As to the "metes and bounds" of the meaning of these portions, it is not believed necessary to define these further. A specific class of antigens has been named and the invention is limited to portions that comprise them. It would clearly be pointless, as the ordinary practitioner would understand, to use fragments that are too small to be effective or which do not contain the appropriate epitopes. If the fragment does not derive from the relevant antigen, it is not included within the scope of the invention. This does not appear indefinite.

Finally, with respect to the phrase "posttranslational modifications different from those of PSA produced in human cells" in claim 35 only, this phrase is added simply to distinguish any coincidental overlap with compositions of the prior art which have included natively produced PSA solely for the purpose of raising diagnostic antibodies. It is believed that the phrase is well understood by those of ordinary skill and need not further be explained.

For the reasons stated above, the rejections under 35 U.S.C. § 112, first and second paragraphs, may properly be withdrawn.

The Art Rejection

Claims 1-40 were rejected under 35 U.S.C. § 103 as obvious over Chu *et al.* in view of Dai *et al.*, Deguchi *et al.*, Brown *et al.* and Alving. This basis for rejection is respectfully traversed.

As a preliminary matter, it is assumed that the Brown *et al.* and Alving references are intended to be applied specifically to claims which are directed to forms of the methods and compositions which involve recombinant

viruses used as vaccines (Brown) or liposomes (Alving). Applicants do not rely on these particular limitations in support of patentability. Applicants do not rely for patentability on the limitation that the active ingredient in the vaccine be supplied as an expression system capable of generating the antigen or portion *in situ*, an embodiment that would include viral vector-based vaccines, or on the use of liposomes. Alving is irrelevant to claims other than claims 17-19, 24-26, 30-32 and 37-39 which require liposomes. Brown is irrelevant to two-thirds of claim 1 and its dependent claims; it is irrelevant to those embodiments utilizing the antigen *per se* or an antiidiotypic antibody. Brown is thus irrelevant to claims 15-20 and 28-40.

This leaves Chu, Dai and Deguchi. Applicants are unable to find any suggestion in any of these references, alone or in combination, that an antigen associated with a tissue type that plays host to a tumor be used as an ingredient in a vaccine. Nor is there a suggestion that such a vaccine would elicit an immune response in the subject harboring the tumor which will, in effect, attack both the host tissue and the tumor that resides there. Not one of the references even alludes to such a possibility.

The Office cites column 6, first paragraph of Chu in support of its position that a suggestion is made for "immune-specific chemotherapy." These words are used in lines 28-30, but refer to protocols quite different from those claimed. What is meant by "immune-specific chemotherapy" is elucidated by reference to the Ghose article at line 31. A copy of the abstract of this article is enclosed for the convenience of the Office. It is evident from this abstract that what is referred to here is a by now well known immunoconjugate approach to deliver toxins specifically to a target. Put in the context of the Chu disclosure, what is suggested by Chu is that antibodies

raised against PSA can be employed in such compositions containing the PSA-specific antibody as the targeting component and a toxin as the active agent. This approach has nothing to do with using PSA or any other antigen to elicit an autologous immune response directed at the prostate.

The portion of Chu at column 7, paragraph 3 is also cited; the "conventional vaccine preparation techniques" however, are used to prepare formulations to elicit diagnostic antibodies against human prostate antigen (see line 47). This does not suggest the use of PSA in a vaccine to elicit a response which will target the subject's own prostate and its resident tumor. As noted above, since extracted and purified human PSA has been used to raise diagnostic antibodies, compositions which contain this particular antigen claimed as compositions *per se* have been excluded. The overlap that would have been present had vaccines containing isolated and purified human native PSA been included in the claims, would have been entirely coincidental and not suggestive of the present invention.

Thus, Chu taken alone clearly fails to suggest the invention as claimed.

With respect to Deguchi, this reference is concerned with precisely the same type of immunoconjugate approach suggested by Chu. It is distinct from the present claims for the same reason as set forth above.

With respect to Dai, the Examiner calls attention to the last sentence in the abstract suggesting an antiidiotypic antibody as having potential value for modulating the immune response of Dunning rat prostate tumor. However, Dai's antibodies are mimics not of a prostate-associated antigen, but rather represent the classical approach of using a tumor-associated antigen. As is clear from the abstract, the initial antigen was a rat

tumor membrane antigen. The antiidiotypic antibodies were raised against monoclonals directed against this tumor-associated moiety. There is no suggestion in Dai that prostate-associated antigens should be used to elicit an immune response or that antiidiotypic antibodies which mimic them should be used to do so.

The three references, therefore, make independent suggestions for alternative approaches to combatting prostate tumors, none of which corresponds to, or suggests, the present invention. Chu and Deguchi both suggest employing immunoconjugates; Dai suggests antiidiotypic antibodies mimicking tumor-associated antigens as opposed to host tissue-associated antigens, i.e., prostate-associated antigens. It is unclear how these publications, either individually or together, suggest the method of the present invention. Certainly combining them does not result in any suggestion other than immunoconjugates are one approach and antiidiotypic antigens with respect to tumor-associated antigens are another.

Since the cited references fail to suggest the invention as claimed, withdrawal of this basis for rejection is believed proper.

Conclusion

The methods and compositions of the invention are fully enabled by the specification; the only objection raised by the Office concerns doubt regarding clinical efficacy. Based on the decision in In re Brana, applicants respectfully submit that this is not a proper basis to doubt applicants' specification.

The specific approach claimed -- administering an antigen related to the host tissue in order to raise an autologous immune response that will be toxic to the tumor -- has not been suggested by any of the references

applied alone or in combination. Therefore, it is believed that claims 1, 4-8, 10-15, 17-22, 24-28, 30-35 and 37-40 are in a position for allowance and passage of these claims to issue is respectfully requested.

Respectfully submitted,

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Antibody-linked cytotoxic agents in the treatment of cancer: Current status and future prospects
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J. NAT. CANCER INST. (USA) , 1978, 61/3 (657-676) CODEN: JNCIA
LANGUAGES: ENGLISH
Antibodies against tumor cell surface antigens have been used as selective carriers of anticancer drugs, which themselves lack selectivity. Although such antibodies have been demonstrated in tumor hosts, xenogeneic antitumor sera should provide larger yields of better-defined antitumor antibodies for therapeutic purposes. This review examined factors that influence the immune response to tumor-associated transplantation antigens (TATA) and the methods for rendering tumor cells more immunogenic. Consideration was also given to techniques for elimination of irrelevant immunoglobulin molecules. These could involve purification of both antitumor sera and TATA fractions for immunization, as well as tailoring of the immunization protocol. Various toxic agents that have been linked to antitumor globulins with retention of agent and antibody activity were tabulated: alkylating drugs, antibiotics, antimetabolites, cell surface agents, protein synthesis inhibitors, and unconventional anticancer agents that selectively convert nontoxic arsenicals or halides into cytocidal derivatives. The methods by which effective conjugates can be produced and their possible mode of action were described for the different types of agents. Several problems inherent in this modality of tumor therapy include: 1) the necessity of binding therapeutically effective amounts of antitumor agent, 2) ensuring of delivery of drug in active form to target sites, 3) avoidance of host reactions to foreign proteins, and 4) possible emergence of resistant tumor cell populations. Antibody-linked cytotoxic agents may find their greatest use in the eradication of small numbers of circulating tumor cells and micrometastases remaining after removal of primary tumors.

EMTAGS:
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DESCRIPTORS:
*cancer chemotherapy (0007524); *cancer antibody (0149833); *tumor antigen (0059785); *metastasis (0030190)

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01601110300 /GENERAL ASPECTS/ Treatment/ Chemotherapy
02616030000 IMMUNOLOGY AND SEROLOGY/ TUMOR IMMUNOLOGY/ Tumor immunotherapy
02603040000 /ANTIBODIES, IMMUNOGLOBULINS/ Classes and subclasses
02616010000 /TUMOR IMMUNOLOGY/ Tumor- and tumor-associated antigens
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